November 15, 1973

Mr. Anil Joshi
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My dear Anil:

A surprise it was! Your gift arrived intact and was received with great pleasure by all of us in the family. As you can see it also brought forth a letter from me, admittedly long overdue and with apologies. No excuses, although you must know that I wouldn't forget to write in due time.

We are working hard in the lab these days with a sense of excitement that we may shortly have some important answers to the question of how hormones activate adenylate cyclase systems. The clue to this mechanism is the role of nucleotides, particularly GTP, in this process. We are fairly certain that GTP acts at a regulatory site that mediates the actions of all hormones operating on adenylate cyclase systems and that the regulatory site is proximal to the catalytic site where ATP is utilized. Based on kinetic analyses of substrate utilization, our tentative conclusion is that GTP probably alters the conformation of the catalytic site in a manner that reduces the inhibitory action of free ATP (uncomplexed with Mg) and increases the binding of Mg at a site involving a crucial sulfhydryl group at the active center. Computer fitting of our glucagon binding data coupled with studies of the effects of sulfhydryl agents on this sulfhydryl group indicates that glucagon induces a change in subunit interaction resulting in increased reactivity of the regulatory site with GTP. We have also discovered a universal "hormone" in the form of Gpp(NH)p, the analogue of GTP. This nucleotide is not metaolized and causes the same increase in rate of adenylate cyclase seen by addition of maximal concentration of hormones in the several types of adenylate cyclases systems we are examining (adrenal, salmon red cell, frog red cell, hepatic membranes, and fat cell membranes). The nucleotide causes the same effects on all these systems. With this nucleotide, we now are getting close, as stated above, to the realization of the final stage in the regulation of adenylate cyclase activity. Hopefully our computer modelling will fit our experimental data in a meaningful manner. If so, we will then be prepared to look at the chemistry of the adenylate cyclase system with a sure background of what we are doing.

Perhaps in five years or so we will have the important answers available on hormone action. Not a long time considering that man has been around for millions of years. Of course we could say that what man didn't know didn't

seem to hurt him. The search for knowledge is a wonderful way of spending your life, even if the final outcome is misunderstood or misused by society at large. We, as scientists, must take that risk. After all, the only unique feature of the human is the ability to integrate information. Considering the total human nerve cell capacity on this planet, it is surprising how long it takes man to achieve a rational approach to an understanding of himself and his relationship to the universe. Sad to state, he hasn't yet learned how to overcome his emotions. War, plague, famine hover around us continuously. Collectively, we should be capable of preventing such catastrophes. The point is that man hasn't learned to use the essential conflict of emotion and reasoning in a constructive manner. So, we see the best of Israel and Arab youth succumbing on the battlefield. Senseless!

I hope that your studies in Bangalore are going fine. I will be visiting Irving Fritz over the Christmas Holidays. It would be wonderful if you can come to Canada in the near future. Meanwhile, keep up your spirits as always.

With fondest regards, I remain

Yours truly,

Martin Rodbell, Ph.D.
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